Genetic Contributions to Labor Pain and Progress

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KEYWORDS

• Genetics • Polymorphism • *OPRM1* • *ADRB2* • Labor pain

KEY POINTS

- Phenotyping labor pain and childbirth experience is extraordinarily complex. Therefore, genotyping to find meaningful associations with labor pain perception and neuraxial analgesic response remains challenging.
- The μ-opioid receptor gene (*OPRM1*) influences pain perception and response to opioids; however, this effect may be different according to the pain modality, the opioid chosen, and the mode of administration.
- The catechol-O-methyltransferase gene (*COMT*) influences pain perception and may impact the response to labor analgesia.
- Studies on the β_2-adrenergic receptor gene (*ADRB2*) demonstrate a slow haplotype (Arg16/Gln27 double homozygosity) that seems to confer protection from preterm labor and delivery but results in prolonged labor.
- The oxytocin receptor gene (*OXTR*) is an obvious candidate in the context of labor and delivery; future studies are likely to find associations with implications for the management of labor pain and obstetric outcomes.

INTRODUCTION

Since the completion of the Human Genome Project more than a decade ago, anesthesiologists and pain specialists have been somewhat disillusioned after the promise that pharmacogenomics would transform their practice and result in personalized medicine.[1–4] Indeed, recommendations based on pharmacogenetic testing to help clinicians tailor regimens for safe and effective anesthesia and analgesia are still awaited. Working toward this translation, the pharmacogenetics research network recently

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established a pharmacogenomics knowledge base (PharmGKB)[5] with the goal "to collect, encode, and disseminate knowledge about the impact of human genetic variations on drug response, curate primary genotype and phenotype data, annotate gene variants and gene-drug-disease relationships via literature review, and summarize important pharmacogenetic genes and drug pathways." Recently formed, the Clinical Pharmacogenetics Implementation Consortium[6] has established clinical recommendations for dosing based on genetic testing for 8 different drugs, out of which only codeine prescription according to the CYP2D6 genotype[7] may be relevant to the practice of anesthesiologists, pain doctors, pediatricians, obstetricians, or perinatologists. In addition, the current body of knowledge on the contribution of genetics on labor pain and analgesia or the progress of labor remains scarce.

This review aims to describe association studies that have examined the influence of variants within 4 genes on labor pain and the response to opioids in laboring women as well as the progress of labor; the genes include the μ-opioid receptor gene (*OPRM1*), the catechol-*O*- methyltransferase gene (*COMT*), the β_2 adrenergic receptor gene (*ADRB2*), and the oxytocin receptor gene (*OXTR*) (**Table 1**). In addition, some of the challenges inherent to the design and conduct of genetic associations studies, such as defining a crisp phenotype and selecting the appropriate candidate genes, is described.

LABOR PAIN AND PROGRESS

Clearly, the pain of childbirth is the most severe pain most women will endure in their lifetimes.[8] The International Association for the Study of Pain emphasized in their 2007–2008 report during the "Global Year against pain in women – real women, real pain"[9] that (1) the importance of treating pain within the pregnant population and the substantial public health impact if pain is neglected, (2) the alarmingly high rate of acute or chronic pain after delivery, and (3) labor pain as a clinical model for studying acute pain. Nonetheless, despite undeniable advances in our understanding of the physiology of labor pain that have resulted in the ability to provide safe and effective labor analgesia to most women in the developed world, evaluating and measuring labor pain and the response to analgesia remains a remarkable challenge.[10] During 9 months of pregnancy, women's expectations regarding the birthing process are extraordinarily diverse and influenced by many factors. In no other field of medicine is the experience of a painful process described in such divergent ways: natural, beautiful, and worthwhile to the point of being exhilarating on the one hand and overwhelmingly painful, horrible, distressing, and traumatic on the other. For the subset of women who know from the start they want to deliver with minimal discomfort by means of an epidural, providing an ideal labor analgesic is currently quite simple to achieve effectively. Nonetheless, for women who are either undecided or think they prefer a natural and unmedicated childbirth, the sense of disappointment and guilt often supersedes the benefits of pain relief if they ultimately fail and request a labor epidural analgesia, no matter how successful the analgesia.[11]

Therefore, it is no surprise when one realizes that a standard tool, such as a numeric pain score, used in all clinical pain studies does not capture very well the essence of labor pain. Other challenges that are specific to obstetric pain relate to the dynamic nature of labor and labor progress and the consequent changes in nociception that occur over time; pain of first-stage labor is conducted by thin afferent, *visceral* sympathetic fibers, entering the spinal cord at thoracic and lumbar roots (T10-L1), whereas second-stage labor pain is conducted via thicker *somatic* nerve fibers entering the spinal cord at sacral roots S2 to S4. The dynamic component of labor pain has